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Review Article

Role of ICH guidelines in registration of Pharmaceutical Products

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Abstract

The International Conference on Harmonization (ICH) of Technical Requirements is a unique project for Registration of Pharmaceutical products which are intended for human use. This brings together the regulatory authorities of Europe, Japan and United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration.

The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines.

The objective of such harmonization is a more economical use of human, animal and material resources and the elimination of unnecessary delay in the global development and availability of new medicines whilst maintaining safeguards on quality, safety and efficacy and regulatory obligations to protect public health. It creates a venue that allows all key pharmaceutical regulatory authorities and industry stakeholders the opportunity to be more actively involved in pharmaceutical harmonization work. It aimed at the standardization of requirements and format along with the content of regulatory documentation and brings down the pressure on the price of medicines by enabling greater economies of scale and a labelled regulatory playing field. This paper is an effort to provide the detailed information about ICH Guidelines.

Keywords: ICH, QSEM, Regulatory, Technical, Harmonization, MedDRA

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1. Introduction

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (1) is a unique project in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development.

Harmonisation leads to a more sensible use of human, animal and other resources, the elimination of unnecessary delay in the global development, and availability of new medicines while maintaining safeguards on calibre, welfare, efficacy, and regulatory obligations to protect public health.

Harmonisation can be achieved through the development of ICH Guidelines via a process of scientific consensus with regulatory and industry experts working side-by-side. The basic key to the success of

this process is the commitment of the ICH regulators to implement the final Guidelines.

The mission of ICH is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration and the maintenance of such registrations. It also monitors and update harmonised technical requirements leading to a greater mutual acceptance of research and development data. ICH helps to facilitate the adoption of new or improved technical research and development approaches which update or replace current practices. It helps to develop policy for the ICH Medical Dictionary for Regulatory Activities Terminology (MedDRA) (2) whilst ensuring the scientific and technical maintenance, development and dissemination of MedDRA as a standardised dictionary which facilitates the sharing of regulatory information internationally for medicinal products used by humans.

Its objectives are, thus, as follows:

- More efficient and effective use of human, animal and material resources
- Reduce the development times and unwanted delays of drugs
- End duplicate clinical trials
- Facilitate the concurrent launch of a new drug in different countries, across all three ICH members
- Create guidelines to ensure that the highest level of safety, quality and efficacy is applied to drug development, with an eye towards globalization.

Structure of ICH (3)

1. ICH Assembly
2. ICH Management Committee
3. MedDRA Management Committee
4. ICH Secretariat

The **ICH Assembly** works in bringing together all Members and Observers of the ICH Association as the overarching governing body of ICH. It takes decisions on particular matters such as on the adoption of ICH Guidelines, admission of new Members and Observers,

and the ICH Association's work plans and budget. Member representatives appointed by the Assembly are supported by ICH Coordinators who represent each Member to the ICH Secretariat on a daily basis.

The **ICH Management Committee (MC)** is that body which supervises the operational aspects of ICH on behalf of all Members, including administrative and financial matters and oversight of the Working Groups (WGs).

The **MedDRA Management Committee (MC)** has responsibility for providing direction of MedDRA, ICH's standardised medical terminology. The MedDRA MC is responsible for managing, supporting, and facilitating the maintenance, development, and dissemination of MedDRA.

The **ICH Secretariat** is responsible for day-to-day management of ICH, coordinating ICH activities as well as providing support to the Assembly, the MC and Working Groups. The ICH Secretariat also provides support to the MedDRA MC. The ICH Secretariat is located in Geneva, Switzerland.

The development of a new harmonised guideline and its implementation (the formal ICH procedure) involves 5 steps (4): (Figure.1)

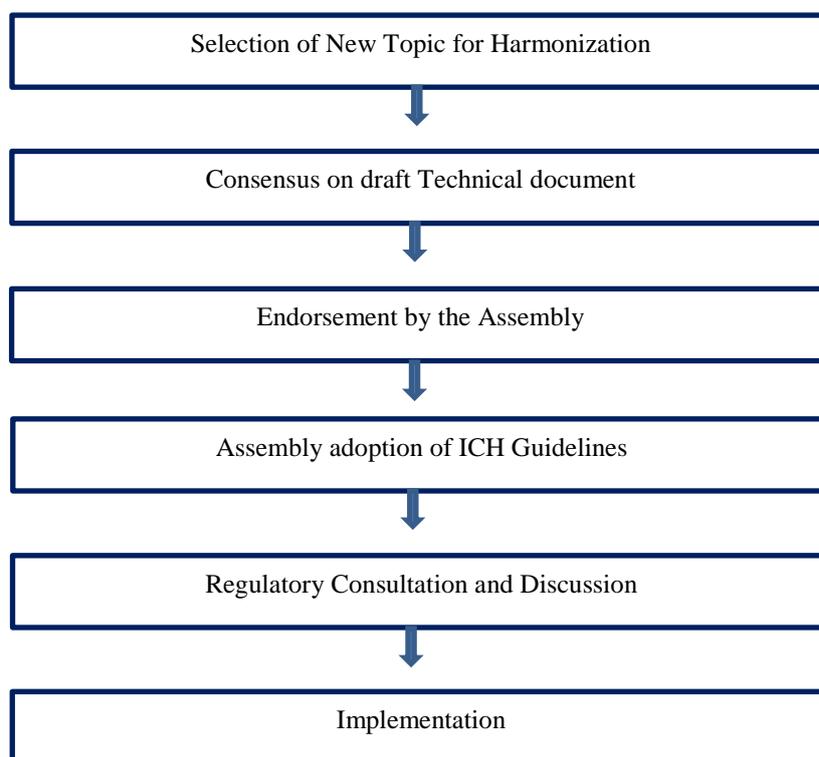


Figure1. Flowchart showing ICH Harmonization Process

ICH Guidelines (5)

The objective of ICH is to increase international harmonization of technical requirements to ensure that safe, effective, and higher quality medicines are developed and registered in the most efficient and cost

effective manner. ICH has developed over 45 harmonized guidelines.

There are four major categories into which the ICH guidelines are divided:

Quality (Q), i.e., those relating to chemical and pharmaceutical Quality Assurance.

Safety (S), i.e., those relating to *in vitro* and *in vivo* preclinical studies.

Efficacy (E), i.e., those relating to clinical studies in human subject.

Multidisciplinary topics (M), i.e., cross-cutting Topics which do not fit uniquely into one of the above categories.

The strength of the ICH process lies in the commitment for implementation by ICH Regulatory Members using appropriate national/regional tools as shown in Figure. 2.

QUALITY	
Stability	Good manufacturing practice
Analytical validation	Pharmacopoeias
Pharmaceutical development	Specifications
Quality risk management	Impurities
Development and manufacture of drug substances	Pharmaceutical quality system
SAFETY	
Carcinogenicity studies	Biotechnology products
Pharmacology studies	Reproductive toxicology
Immunotoxicology studies	Photosafety evaluation
Nonclinical evaluation for anticancer pharmaceuticals	Toxicity testing
Genotoxicity studies	Toxicokinetics and Pharmacokinetics
EFFICACY	
Clinical safety	Clinical trials
Clinical study reports	Clinical evaluation by therapeutic category
Dose-response studies	Clinical evaluation
Ethnic factors	Pharmacogenomics
Good clinical practice	
MULTIDISCIPLINARY	
MedDRA terminology	Data elements and standards for drug
Electronic standards	Dictionaries
Nonclinical safety studies	Gene therapy
CTD and eCTD	Genotoxic impurities

Figure 2. ICH Guidelines- QSEM

Guidelines

The present study is an attempt to provide detailed information about ICH on the basis of literature.

2. Quality

Stability Testing

The objective of stability study (6) is to provide proof on how the quality of drug substance or drug product changes with time under the effect of a variety

of environmental factors such as temperature, humidity and light and recommended storage conditions, re-test periods and shelf-life to be established. The choice of test conditions depends on climatic conditions in the areas of EU, JAPAN and USA.

Drug substance

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

Stress study of the drug substance can help identify the degradation products which can in turn help establish the degradation pathways and validate the stability indicating power of the analytical procedures used. (7) The nature of the stress study will depend on the individual drug substance and the type of drug product used.

Stress study is to be carried out on a single batch of the substance. It should include the effect of temperature, humidity. The study should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability study should be an integral part of stress testing. (8) The standard conditions for Photostability studies are described in ICH Q1B. (9)

Data from formal stability studies should be provided on at least three batches. The batches should be manufactured to a pilot scale by the same route as used earlier and using a method of manufacture and procedure that simulates the final process for production batches.

The stability studies should be conducted on the drug substance packed in final packing. Specification is a list of tests, reference to analytical procedures and proposed acceptance criteria, which are addressed in ICH guideline Q6A and Q6B. Additionally, specification for degradation of products in a drug substance is discussed in Q3A.

Stability studies include study of those of attributes of the drug substance that are susceptible to change during storage and are likely to affect quality, safety and efficacy. The study should cover, as appropriate, the physical, chemical, biological and microbiological attributes. Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies. (10)

Study frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the Active Pharmaceutical Product (API). For APIs with a proposed re-test period or shelf-life of at least 12 months, the frequency of testing at the long-term storage condition should normally be in every three months over the first year, in every six months over the second year, and annually thereafter throughout the proposed re-test period or shelf-life.

At the accelerated storage condition, a minimum of at least three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six months study is recommended.

When a testing at the intermediate storage condition is required as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

Storage conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its 91 sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and relative humidity of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines, in table 1, table 2 and table 3.

Table 1 General case

STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
Long-term	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months
Intermediate	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

Table 2 Active pharmaceutical ingredients intended for storage in a refrigerator

STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
Long-term	5 °C ± 3 °C	12 months
Accelerated	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

If significant change occurs between three and six months testing at the accelerated storage condition, the proposed re-test period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual.

It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

Table 3 Active pharmaceutical ingredients intended for storage in a freezer

STUDY	STORAGE CONDITION	MINIMUM TIME PERIOD
Long-term	-20 °C ± 5 °C	12 months

In the rare case of any API of non-biological origin being intended for storage in a freezer, the re-test period or shelf-life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. 5 °C ± 3 °C or 25 °C ± 2 °C or 30 °C ± 2 °C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

Active pharmaceutical ingredients intended for storage below -20°C

APIs intended for storage below -20 °C should be treated on a case-by-case basis.

Evaluation

The purpose of the stability study is to establish and evaluate the stability information including, as appropriate, results of the physical, chemical, biological and microbiological tests, a re-test period applicable to the other batches of the API manufactured under similar circumstances. The degree of discrepancy of an individual batch affects the conviction that a future production batch will remain within specification throughout the assigned re-test period.

Ongoing stability studies

The stability of the API should be monitored on the basis of continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The ongoing stability programme is required to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the re-test period in all future batches.

The ongoing stability programme should be described in a written protocol and the results are presented in a formal report.

The protocol for an ongoing stability programme should extend to the end of the re-test period and shelf-life and should include the following parameters:

- number of batches and batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing frequency;
- description of the storage conditions (standardized conditions for long-term testing as described in

these guidelines, and consistent with the API labelling, should be used);

- Other applicable parameters specific to the API.

Validation

Validation of an analytical procedure is the process by which it is established, by laboratory studies so that the performance characteristics of the procedure meet the requirements for the intended analytical applications. Method validation provides an assurance of reliability during normal use, and is sometime referred to as “the process for providing documented evidence that the method does what it is intended to do.” (11)

The main objective of the validation is to demonstrate that the analytical method is suitable for its intended purpose, is accurate, specific and precise over the specified range that an analyte will be analysed. Analytical Method Validation is to be performed for new analysis methods or for current methods when any changes are made to the procedure, composition of the drug product and synthesis of the drugs substances.

Typical validation characteristics which should be considered are listed below (12):

- **Accuracy:** The accuracy of an analytical method is defined as the closeness of the test results obtained by that method to the true value. This is sometimes termed trueness. The accuracy can be determined by using a minimum of nine determinations over a minimum of the three concentration levels, covering a specified range.
- **Precision:** The precision of an analytical method is defined as the degree of agreement among individual test results when the method is repeated to multiple samplings of a homogeneous sample. (13) The precision of an analytical procedure is usually determined as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements.

i) Repeatability

Repeatability is termed as the use of the analytical procedure within a laboratory over a short period of time using the same analyst with the same equipment. It should be evaluated using a minimum of nine determinations covering the specified range for the procedure (i.e., three concentrations and three replicates of each concentration or using a minimum of six determinations at 100% of the test concentration).

ii) Reproducibility

Reproducibility indicates the precision between laboratories (collaborative studies, usually applied to standardisation of methodology). It is usually demonstrated by means of an inter-laboratory trial.

- **Specificity:** Specificity is the ability to measure accurately and specifically the analyte of interest in the presence of other components that may be expected to be present in the

sample matrix such as contaminant, foreign particles, degradation products and matrix components. It must be demonstrated that the analytical method is unaffected by the presence of spiked materials (impurities and/or excipients).

In case of identification tests, the method should be able to discriminate the compounds of closely related structures which are likely to be present. Similarly, in case of assay and impurity tests by chromatographic procedures, specificity can be demonstrated by the resolution of the two components which elute closest to each other.

- **Linearity:** It is a mathematical relationship or function which means that it can be graphically represented as a straight line. It can be established initially by visual examination of a plot of signals as a function of analyte concentration of content. It is suggested to have a minimum of five concentration levels, along with certain minimum specified ranges. For performing the assay, the minimum specified range is from 80% -120% of the target concentration.
- **Detection Limit and Quantitation Limit:** The Detection Limit refers to the lowest concentration of an analyte in a sample that can be detected but cannot be quantified. The Quantitation Limit refers to the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operational conditions of the analytical procedures.

The basic approaches to determine the Detection Limit and Quantitation Limit are:

- i) **Visual Evaluation:** Visual evaluation may be used for non-instrumental methods. It is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected. The quantitation limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be determined with acceptable accuracy and precision.
- ii) **Signal to Noise:** This type of approach can only be applied to analytical procedures that show baseline noise. Determination of the signal-to-noise ratio is carried out by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and also establishing the minimum concentration at which the analyte can be reliably detected for the determining the Detection Limit and reliably quantified for the determining the Quantitation Limit.

A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit and a typical signal-to-noise ratio is 10:1 is considered for establishing the quantitation limit.

- **Range:** The range of an analytical procedure is the interval between the upper and lower levels of analyte that have been demonstrated to be determined with a suitable level of exactness, accuracy and linearity using the procedure as written.

The following minimum specified ranges should be considered:

1. For assay of a drug substance, the range should be from 80% to 120% of the test concentration.
 2. For determination of an impurity: from 50% to 120% of the acceptance criterion.
 3. For Content Uniformity: a minimum of 70% to 130% of the test concentration, unless a wider or more appropriate range based on the nature of the dosage form (e.g., metered-dose inhalers) is justified.
 4. For Dissolution Testing: $\pm 20\%$ over the specified range.
- **Robustness:** The robustness is defined as a measure of the capacity of the analytical procedure to remain unaffected by small but deliberate variations in procedural parameters listed in the procedure documentation and provides indication of its suitability during normal usage. It may be determined during development of the analytical procedure.

If the quantifications are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure.

Good Manufacturing Practices

Good manufacturing practices (GMP) is a part of Quality Assurance (QA) which ensures that products are consistently produced and controlled in accordance with the quality standards that are appropriate for their intended use and as required by the marketing authorization. (14) GMP guidelines provide minimum requirements for pharmaceutical or a food product manufacturer to assure that the products are of high quality and do not pose any risk to the consumer.

Additionally, GMP has issued guidelines for the achievement of consistent product quality, with interpretation and individual variations being accepted. GMP implemented in the United States by the US FDA, under Section 501(B) of the 1938 Food, Drug, and Cosmetic Act (21 USCS § 351). The regulations use the phrase "current good manufacturing practices" (cGMP) and it describes the guidelines. (15)

Pharmacopoeia

A Pharmacopoeia is a legally binding collection of standards and quality specifications for medicines used in a country or region. (16) Within the pharmacopoeia, a quality specification is a set of appropriate tests that will confirm the identity and purity of the product, ascertain the strength (or amount) of the active substance and, when needed, the performance characteristics. Reference substances that are used in testing help to ensure the quality, strength and purity of the drugs. A pharmacopoeia covers the information regarding the pharmaceutical starting materials, excipients, intermediates and finished pharmaceutical products (FPPs). Details of general requirements may also be provided on important subjects related to drugs quality, such as analytical methods, microbiological purity, dissolution testing, or stability.

The modern pharmacopoeia points out certain quality specifications for active pharmaceutical ingredients (APIs), FPPs and general requirements. The existence of such specifications and requirements is necessary for the proper functioning or regulatory control of medicines production.

Specifications

The specifications are to assure that each unit has the value of drug claimed on the label, that all the drug in each unit is out there for whole use, that the drug is steady within the formula in its certain final container for their expected shelf life and it's having no toxic overseas substance. (17) It is greatly used in pharmaceutical enterprise and also utilized by using wellness sector and support best which is finished via GMP, GLP and GCP and other organization including Pharmaceutical Quality System (PQS), Quality Risk Management (QRM) and Quality by Design (QbD).

The objectives of specification arrangements are- (1) to identify appropriate and safe limits or quantitative ranges during clinical development and (2) to give specifications for the product to enter the market. One of the most difficult challenges in establishing and consequently giving specifications is achieving the appropriate balance among all factors including human safety, health and efficacy, scientific proven data, analytical variability, process knowledge and capability, regulatory requirements, and business issues. (18)

3. Safety

Carcinogenicity Studies (S1A-S1C)

Carcinogenicity studies may be needed to support marketing approval for some botanical drug products. This depends on the chronic use of the drug, or specific causes for concern. However, the need and the timing relative to clinical development of carcinogenicity studies can be impacted by the toxicity profile of the botanical drug, indications, and duration of the intended use in humans. (19)

S1A: Guidelines on the need for carcinogenicity studies of pharmaceuticals

Carcinogenicity studies can be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months.

This document provides a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs. These recommendations focus on the known risk factors as well as the intended indications and duration of exposure.

The goal of carcinogenicity studies is to identify a tumorigenic potential in animals and to assess the relevant risk in humans.

S1B: Testing for carcinogenicity of pharmaceuticals

This document provides guidance on the need to carry out carcinogenicity studies in both mice and rats, and guidance also given on alternative testing procedures which may be applied without jeopardizing safety.

S1C (R2): Dose selection for carcinogenicity studies of pharmaceuticals

This document addresses the criteria for the selection of the higher dose to be used in carcinogenicity studies on new therapeutic agents to harmonize the current practices and improve the design of studies.

Genotoxicity

Genotoxicity is the study of chemical agents that damages the genetic information within a cell causing mutations, which may lead to cancer. (20) The genotoxicity testing is used to determine if a substrate will influence genetic material or it may cause cancer. They can be performed in bacterial, yeast, and mammalian cells. One can control early development of vulnerable organisms to genotoxic substances from the result of the test.

S2(R1): Guidance on testing and data interpretation for pharmaceuticals intended for human use

This guidance is generated as a result of combination of ICH S2A and S2B guidelines.

S2A: Guidance on specific aspects of regulatory genotoxicity tests for pharmaceuticals

This document provides specific guidance and recommendations for *in vitro* and *in vivo* tests and also on the evaluation of the test results. It encompasses the terms related to genotoxicity tests to improve consistency in applications.

S2B: A standard battery for genotoxicity testing for pharmaceuticals

This document addresses two fundamental areas of genotoxicity testing (21):

- The recognition of a standard set of assays to be conducted for registration and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.
- Registration of pharmaceuticals requires a comprehensive assessment of their genotoxic potential. It is a fact that no single test is capable of detecting all relevant genotoxic agents. Therefore, the usual approach should be

carried out on a battery for *in vitro* and *in vivo* tests for genotoxicity.

The main purpose of this guideline is to optimize the standard genetic toxicology battery for forecast the potential human risks and for interpretation of results with the ultimate goal of improving the risk characterization for carcinogenic effects that have their basis in changes in the genetic material.

S3A-S3B Toxicokinetics and Pharmacokinetics:

- Toxicokinetic studies are not required to be conducted, except in pregnant, lactating animals, before initiating reproductive studies according to ICH guidelines.
- Toxicokinetics is defined as the generation of pharmacokinetic data, either as an integral component in the conduct of non-clinical toxicity studies or in specially designed supportive studies, in order to assess systemic exposure. (22)

This document provides guidance on developing test strategies in toxicokinetics and the need to integrate the pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and their relevance to clinical safety issues.

The primary objective of toxicokinetics study is to describe the systemic exposure achieved in animals and its relationship to dose level and the time period of the toxicity study.

S3B: Pharmacokinetics: Guidance for repeated dose tissue distribution studies

- Tissue distribution studies are helpful in providing information on distribution and accumulation of the compound and metabolites, especially in relation to potential sites of action. This information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments. (23)
- This document provides the guidance, when the repeated dose tissue distribution studies should be considered (i.e., when appropriate data cannot be derived from other sources).

S4: Time span of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)

The objective of this guidance is to set out the considerations that apply to chronic toxicity testing in rodents and non-rodents as part of the safety evaluation of a medicinal product.

- Rodents (a study of 6 months duration)
- Non-rodents (a study of 9 months duration)

S5: Detection of toxicity to reproduction for medicinal products and toxicity to male fertility

- This document provides guidance on tests for reproductive toxicity. (24)
- It defines the period of treatment to be used in animals in order to reflect the better exposure of

human to medical products and allow more specific identification of stages at risk.

- It should persuade the evaluation on the safety of chemicals on the development of the offspring.

S6: Preclinical Safety Evaluation of Biotechnology-derived pharmaceuticals (25)

These guidelines include the pre-clinical safety testing requirements for biotechnological products. It addresses the use of animal models of diseases, determination of genotoxicity assays and carcinogenicity studies should be performed and the impact of antibody formation during toxicology studies.

The primary goals of preclinical safety evaluation are:

- To identify a commencing dose and subsequent dose in humans.
- To identify probable target organs for toxicity and for the study of whether such toxicity is reversible.
- To identify safety parameters for clinical monitoring.

S7A: Safety Pharmacology studies for Human Pharmaceuticals (26)

- This guideline was developed in order to protect the clinical trial participants and patients receiving marketed products from potential adverse effects of pharmaceuticals.
- This document addresses the definition, objective and scope of safety pharmacology studies.
- It also addresses which studies are required before the initiation of Phase I clinical trials as well as the information needed for marketing of the pharmaceuticals which are intended for human use.

S8: Immunotoxicity studies for human pharmaceuticals (27,28)

- This guideline addresses the recommendations on nonclinical testing for immunosuppressant.
- This guideline might also apply to drugs in which clinical signs of immunosuppressant are observed during clinical trials and following approval to market.
- The term immunotoxicity is primarily refers to immunosuppressant, i.e. a state of increased susceptibility to infections or the development of tumors.

S9: Nonclinical Evaluation for Anticancer Pharmaceuticals

- This guideline provides information of the pharmaceuticals that are only intended to treat cancer in patients with late stage or advanced disease regardless of the route of administration, including both small molecule and biotechnology-derived pharmaceuticals.

- The main objective of this guideline is to facilitate and accelerate the development of anticancer pharmaceuticals and to protect patients from unnecessary adverse effects, while avoiding unnecessary use of animals and other resources.

S10: Guidelines- Photo safety evaluation of pharmaceuticals (29)

- These guidelines applied to new APIs. New excipients clinical formulations for dermal application and photodynamic therapy products.
- It's an unified process that can involve an evaluation of photochemical characteristics, data from non-clinical studies and human safety information.
- The photo safety assessment aims to determine whether risk minimization measures are warranted to prevent adverse events in humans.
- *In-vitro* assay for photo-toxicity is the 3T3 neutral red uptake assay. (30)
- *In-vivo* assay for species selection, irradiation sensitivity, heat tolerance, performance of reference substance should be considered.

S11: For Non-clinical safety testing in support of development of paediatric medicines

- This guideline is needed to recommended standards for the conditions under which non-clinical juvenile animal testing is considered informative and support paediatric clinical trials.
- The expert working group (EWG) will consist of two non-clinical experts nominated by EU, EFPIA, FDA, MHLW, JPMA, PhRMA, HEALTH Canada and Swiss medic. Anyone of the member can also be nominated by WHO Observer, as well as RHIs, DRAs/doH.

4. Efficacy

The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines.

Efficacy guidelines

- ✓ Clinical safety E1-E2F
- ✓ Clinical study reports E3
- ✓ Dose response studies E4
- ✓ Ethnic factors E5
- ✓ Good clinical practice E6
- ✓ Clinical trials E7-E11
- ✓ Guidelines for clinical evaluation by therapeutic category E12
- ✓ Clinical evaluation E14

- ✓ Pharmacogenomics E15-E16
- ✓ Joint safety/ Efficacy Topic M3

E1: The Extent of Population Exposure to Assess the Clinical Safety for Drugs that are intended for Long-Term Treatment of Non-Life Threatening Conditions

This document gives endorsement on the numbers of patients involved and duration of exposure for the safety evaluation of drugs intended for the long-term treatment of non-life-threatening conditions.

Events where the rate of occurrence changes over a longer period of time may need to be specify depending on their severity and importance to the risk-benefit assessment of the drug.

E2A-E2F: Pharmacovigilance (31)

Pharmacovigilance (PV) is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term as well as short term side effects of medicines. PV is a crucial and fundamental part of clinical research.

E2A- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

There are two different types of issues within the broad subject of clinical safety data management that are appropriate for harmonization at this time:

- The development of standard definitions and terminology for key aspects clinical safety reporting.
- The suitable mechanism for handling expedited (rapid) reporting in the investigational (i.e. pre-approval) phase.

E2B(R2) - Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

To standardize the details of the data for transmission of individual case safety reports by identifying and where necessary or advisable, by defining the data elements for the transmission of all types of individual case safety reports, regardless of source and destination.

E2B(R3) Q & As Implementation: Electronic Transmission of Individual Case Safety Reports

E2C(R2) Clinical Safety Data Management: Periodic safety update Report for marketed drugs E2C (R1)

These documents include guidance on the format and content of safety updates which are needed to be provided at different intervals to the regulatory authorities after products have been marketed. This guideline aims to ensure whether the worldwide safety experience is provided to authorities at defined times after marketing with maximum efficiency and avoiding duplication of efforts.

E2C (R2): This revision was endorsed by Steering Committee in Dec. 2010. It is mandatory for evaluating the ICH Pharmacovigilance documentation, conduct a gap and potential improvement analysis of ECH E2C,

E2E and E2F and draft a new ICH E2C R2 covering periodic benefit risk evaluation reporting.

E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

- This provides a standardized procedure for post-approval safety data management including expedited reporting to relevant authority.
- The definitions of the terms and concept specific to post-approval phase are also included in this type of guidelines.

E2E Pharmacovigilance Planning (32)

It is responsible for the Planning of pharmacovigilance activities, especially in preparation for the early post marketing period of a new drug (chemical entities, biotech-derived products, vaccines).

Main focus: Safety specification and PV plan that might be submitted at the time of license application.

E2F Development Safety Update Report

The DSUR principally focuses on knowledge from interventional clinical trials of investigational medication together with biologicals. It's freelance of the actual fact that whether or not it's, with or while not a promoting approval or conducted by industrial or non-commercial sponsors.

It is applicable to the periodic news on medication beneath development (including marketed drugs that are under further study) among the ICH regions.

E3: Structure and content of clinical study reports

It is a closed or compact report of a personal safety for any therapeutic, prophylactic or diagnostic agent conducted in patients, within which the clinical and applied mathematics description, displays and analyses area unit integrated into one report. These reports area unit created easier to check incorporating tables and figures into the most text of the report or at the tip of the text and with appendices containing the protocol, sample case reports forms, investigators related information, information related to the test drugs/investigational products, including active control/comparators, technical statistical documentation, related publications, patient data listings, and other technical statistical details such as derivations, computations, analyses, and computer output etc.

E4: Dose-response data to support drug registration

- The safe and effective use of medicines in patients depends upon the information of the relationships among dose, drug concentration in blood and clinical response. The effectiveness and undesirable effects area unit vital for ideas of minimum effective dose and most helpful dose that do not adequately account for individual variations and don't enable a comparison, at numerous doses, of each helpful and undesirable effects.
- Any given dose provides a combination of fascinating and undesirable effects, with no single dose essentially best for all the patients.

E5 R1: Ethnic factors within the Acceptability of Foreign Clinical Knowledge

This document provides the intrinsic characteristics of the drug recipient and extraneous characteristics related to atmosphere associated and culture that would have an effect on the results of the clinical studies dole out in regions and describes thought of the "bridging study" (33) that a new region could request to see whether or not knowledge from another region area unit applicable to its population.

E6 R1: Good Clinical Practice (34)

The responsibilities and expectations of all participants within the conduct of clinical trial together with the investigators, monitors, sponsors and IRBs are represented through this document.

GCPs cowl aspects of monitoring, reporting and archiving of clinical trials and incorporating addenda on the Essential Documents (35) and on the Investigator's Brochure which had been agreed earlier through the ICH process.

E7: Studies in Support of special populations: Geriatrics

This document provides recommendations on the special issues that apply within the design and conduct of clinical trials of medicines that are likely to have significant use in the elderly.

It requires special consideration due to the frequent prevalence of underlying diseases, concomitant drug therapy and therefore the resultant risk of drug interaction.

E8: General issues of clinical trials

The general scientific principles for the conduct, performance and management of clinical trials are sets out via this document.

The guideline addresses a good vary of subjects in the design and execution of clinical trials.

E9: Statistical principles for clinical trials

These biostatistical tips are essential for issues on the planning and analyses of clinical trials, particularly the "confirmatory" (hypothesis-testing) trials that are the basis for demonstrating effectiveness.

The document will assist scientific consultants charged with making ready application summaries or assessing proof of efficacy and safety, principally from clinical trials in later phases of development.

E10: Choice of control group and related issues in clinical trials

This document recommends the selection of control group in clinical trials considering the ethical and inferential properties and limitations of various kinds of control groups. It points out the assay sensitivity drawback in active control equivalence/ non-inferiority trials that limit the utility of trial design in several circumstances.

E11: Clinical investigation of medicinal products in the paediatric population (36)

This document addresses the conduct of clinical trials of medicines in paediatric populations. This document will facilitate the event of safe and effective use of medicinal product in paediatrics.

E12: Principles for clinical evaluation of new antihypertensive drugs

It provides a collection of “principles” on which there’s general agreement among all the three ICH regions covering endpoints and trial designs.

It will not be subject to the same old procedures leading to a completely harmonical document.

E14: The clinical analysis of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic medication

- This document provides steering to sponsor the evaluation concerning the planning, conduct, analyses and interpretation of clinical studies to assess the potential of a drug so as to delay cardiac repolarisation.
- This assessment ought to embody testing the consequences of latest agents on the QT/QTc interval. The QT interval could be a activity made on an electrocardiogram used to assess some of the electrical properties of the heart. It is calculated as the time from the start of the Q wave to the end of the T wave, and approximates to the time taken from when the cardiac ventricles start to contract to when they finish relaxing.
- The assessment of the effects of drugs on cardiac repolarisation is the subject of active investigation.

E15: Definitions for genomic biomarkers, pharmacogenomics, genetic science, genomic knowledge and sample coding categories

Pharmacogenomics and genetic science are the terms that have the potential to enhance the discovery, development and use of medicines.

5. Multidisciplinary Guidelines

MedDRA Medical Dictionary for Regulatory Activities

The development of a Medical Dictionary for Regulatory Activities was approved by the ICH Committee in 1997 and also the nomenclature launched in 1999.

In November 2016, the Board approved the Working Group’s Concept Paper on the extension of the remit for the M1 PtC WG. (37) This proposal aims to develop and maintain a companion document to the PtC documents, available in English and Japanese, which might give more detailed guidance, examples, explanations and answers on bound topics of regulatory importance such as data quality, medication errors and product quality issues.

ESTRI-Electronic Standards for the Transfer of Regulatory Information

The M2 Expert Working Group (EWG) was established by the ICH Steering Committee in 1994 with the objective of facilitating international electronic communication by evaluating and recommending, open and non-proprietary (to the extent possible) Electronic Standards for the Transfer of Regulatory Information (ESTRI) that will meet the requirements of the pharmaceutical companies and regulatory authorities.

The M2 EWG has been involved in a number of activities including: recommendation for use by ICH of various open international standards (M2 Recommendations); ICH development of specifications for electronic messages for the E2B(R2) ICH Guideline on Clinical Safety Data Management Data Elements for Transmission of Individual Case Safety Reports, as well as the M4 Common Technical Document (CTD) (38); and the provision of technical input to the ICH E2B(R3) and M5 EWGs in their activities for the advancement of their respective standards through the Standards Development Organisation (SDO) process.

M3 Nonclinical Safety Studies (39)

M3(R2) Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals

M3(R2) Q&As R2 Questions & Answers: Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for prescribed drugs.

M4 Common Technical Document

The Common Technical Document (CTD) was collaborated by the Steering Committee in November 2000.

The Common Technical Document (CTD) could be a set of specification for application dossier for the registration of pharmaceuticals and intended to be used across the three regions - Europe, Japan and the United States. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and also the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals that is intended for Human Use (ICH). The CTD was designed thus on offer a common dossier filing format between U.S, Japan and European countries for the registration of new drug product.

M5 Data Elements and Standards for Drug Dictionaries

In November 2003, ICH Steering Committee endorsed a Concept Paper for M5 guideline and subsequently formed M5 Expert Working Group (EWG) to develop ICH requirements for the standardisation of healthful product identifiers and related terminology. In particular, a need was identified to harmonise product data that might facilitate the electronic exchange of Individual Case Safety Reports (ICSRs) within and across ICH regions using the ICH E2B format in post-marketing pharmacovigilance.

In May 2005, an M5 consensus draft Guideline containing ICH business requirements for medicinal product identifiers, along with lists of controlled vocabularies for Routes of Administration and Units of Measurements, was revealed for public consultation at Step 2 of the ICH process.

The M5 draft Guideline, updated to replicate feedback from the general public consultation, was afterward submitted to the International Organization for Standardization (ISO) for development of electronic communication specifications in February 2007. Work was conducted as a joint initiative with many different SDOs, together with Health Level 7 (HL7), and varied global stakeholders, including experts with experience on the ICH M5 EWG, were active participants. Abbreviated regional testing was performed by the ICH Parties and five International Standards for Identification of Medicinal Products (IDMP) were finalized and revealed by ISO in November 2012. These five ISO standards not solely meet the initial ICH desires for electronic exchange of ICSRs in post-marketing pharmacovigilance, but also support broader functionality.

M6 Virus and Gene Therapy Vector Shedding and Transmission

This new topic was supported by the ICH Steering Committee in September 2009.

In September 2009, following the finalization by the ICH Gene Therapy Discussion Group (GTDG) of the ICH Consideration document "General Principles to deal with Virus and Vector Shedding", the ICH Steering Committee supported the event of associate ICH Guideline on this subject with the aim of providing more extensive information to improve harmonisation amongst the ICH regions. This new topic was subsequently assigned the code "M6". In April 2011, this topic was ceased following SC discussion that concluded due to the current state of science and related resource allocation would not allow this to be supported as a topic for harmonisation.

M7 Mutagenic impurities

M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

M7(R2) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk.

M8 Electronic Common Technical Document (eCTD) (40)

ICH M8 EWG was formed in Nov 2010 to take over the development and revision of eCTD v4.0 Implementation Guide and related documents from the ICH M2 eCTD Subgroup. The eCTD v4.0 requirements were addressed by the Standard Development Organisation process and are included in the Health Level Seven Version 3 Regulated Product Submission Release 2 Normative standard.

The M8 EWG provides technical review and impact assessment of problems arising from the utilization of the ICH M4 CTD Guidelines within the context of the eCTD. This activity includes associate update of M4 Annex: Granularity Document in accordance with the agreement by applicable M4 Working Group whereas the Granularity Document continues to be owned by M4.

ICH M8 IWG was established in conjunction with the formation of M8 EWG in Nov 2010, and assumed the responsibility for the implementation and maintenance of eCTD and Study Tagging File specifications from the ICH M2 eCTD Subgroup. The IWG is also responsible for implementation and maintenance of different M8 EWG deliverables (e.g., Specification for Submission Format for eCTD).

M9 Biopharmaceutics Classification System-based Biowaivers

This topic was supported by the ICH Management Committee in October 2016.

This new multidisciplinary guideline is projected to contend with Biopharmaceutics Classification System (BCS)-based biowaivers. BCS-based biowaivers may even be applicable to BCS Class I and III drugs, but BCS-based biowaivers for these two classes are not recognized worldwide. This implies that pharmaceutical companies have to be compelled to follow different approaches within the different regions. This guideline will provide recommendations to support the biopharmaceutics classification of medicinal products and can offer recommendations to support the waiver of bioequivalence studies. This can lead to the harmonisation of current regional guidelines/guidance and support economical global drug development.

M10 Bioanalytical Method Validation

This topic was endorsed by the ICH Management Committee in October 2016.

This new multidisciplinary guideline addresses to the validation of bioanalytical methods and study sample analyses in non-clinical and clinical studies. This guideline will provide recommendations on the scientific regulatory requirements for bioanalysis conducted during the development of drugs of both chemical and biological origins. It will also address issues on method validation by considering the characteristics of the analytical methods used in bioanalysis, e.g., chromatographic assay and ligand binding assay. A harmonised Bioanalytical method validation guideline will promote the rational and effective non-clinical and clinical studies, thereby advancing the mission of the ICH.

M11 Clinical electronic Structured Harmonised Protocol (CeSHaP)

This topic was endorsed by the ICH Management Committee in November 2018.

This new guideline is proposed to provide comprehensive clinical protocol organization with standardised content, with both required and optional

components. The guideline will outline two main sets of harmonised approaches:

- a template, that include identification of headers, common text and a set of data fields and terminologies which will be the basis for efficiencies in data exchange.
- a technical description, that uses an open, non-proprietary standard to enable electronic exchange of clinical protocol information.

M12 Drug Interaction Studies

This topic was endorsed by the ICH Assembly in June 2018, and an informal Working Group was established in June 2019 to develop a Concept Paper and Business Plan.

6. Conclusion

The ICH is a major global undertaking to affect the harmonization of regulatory requirements in the 3 major regions involved. The creation of the ICH – the International Conference of Harmonization, was fuelled by trade reasons, to even out the competition between markets and end the aforementioned stagnation. ICH was created to deliver health care technology providers a common, almost global regulatory framework for them to develop their products. The ICH's work is far from over, as more and more regulatory scrutiny is demanded from manufacturers and investigators and more pressure is applied to Pharmaceutical companies to increase data transparency, who look up for ICH's guidance.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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